

EDITORIAL COMMENT

Rear-View Mirror Observations on Bleeding in Acute Coronary Syndromes*

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Human beings, who are almost unique in having the ability to learn from the experience of others, are also remarkable for their apparent disinclination to do so.

—Douglas Adams, *Last Chance to See* (1)

Large-scale registries continue to provide useful information regarding the contemporary management of acute myocardial infarction. Moreover, given the plethora of major advances in pharmacological therapy, coupled with the increasing momentum toward early invasive study and coronary intervention, they provide an instructive rear-view window into how the results of clinical trials are embraced (or not) by the medical community. Hence, in this issue of *JACC: Cardiovascular Interventions*, the observations from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry of Kadakia et al. (2) in over 100,000 patients studied between January 2007 and June 2009 give us a fresh and informative look at the use of anticoagulants across the spectrum

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of acute coronary syndrome (ACS) patients. Their data, provided herein, from this important cohort of whom approximately two-thirds were non-ST-segment elevation myocardial infarction (NSTEMI), convincingly demonstrate that the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding risk score acquired from key baseline variables reliably tracks the occurrence of major bleeding in both NSTEMI

and ST-segment elevation myocardial infarction (STEMI) patients (3).

The study also reveals several interesting and remarkable paradoxes: 1) despite repeated demonstration of the superiority of alternate anticoagulant regimens over conventional unfractionated heparin, this venerable therapeutic standard remains the most commonly used agent as represented in two-thirds of the STEMI and nearly one-half of the NSTEMI patients; 2) despite the known bleeding hazards of low molecular weight heparin in elderly patients (of whom many were female) and those with diminished renal function, this agent proved to be the most common anticoagulant employed in this very same subset; 3) although within patient “crossover” of anticoagulant therapies is known to be associated with excess bleeding, this pattern of joint usage seems to persist, not only as it relates to concomitant unfractionated and low molecular weight heparin but, interestingly, also with bivalirudin. However, the supplementary data tables do not permit specification as to which additional anticoagulant was used. Finally, not surprisingly, the uptake of bivalirudin shows a steady rise in both STEMI and NSTEMI patients beginning in the third quarter of 2007 (4–6). It is not surprising, however, that there was concomitant use of glycoprotein IIb/IIIa platelet inhibitors in nearly one-half of the STEMI patients and one-quarter of the NSTEMI cohort without supporting evidence (7,8). Overall, major bleeding seems distressingly common among this large cohort of patients averaging approximately 9% in the NSTEMI and 12% in the STEMI groups with a remarkable 6-fold spread in incidence as defined by the CRUSADE bleeding score derived from baseline variables (3).

Although Kadakia et al. (2) assert that the bleeding they have characterized is “largely based on differences in baseline characteristics, comorbidities, and invasive treatment strategies rather than specific anticoagulant regimens” we consider this premise tentative. Further knowledge about the timing of anticoagulant therapy commencement; its dose and duration; the frequency of medication errors; and how the inevitable variety of dynamic changes and comorbidities, such as renal function unfolding after the index event, affected the management of this group of patients would help illuminate this issue (9). Moreover, the absence of registry data on the prior use of antiplatelet agents, such as aspirin and clopidogrel, as well as the timing of concomitant antiplatelet therapy (and its dose) are gaps in the current report that would also be expected to further inform on the occurrence of bleeding. Other key variables that are necessary to provide more context include the vascular access site for coronary intervention, the location of major bleeding, and how frequently blood transfusion was employed (4). Indeed, without knowing the longer-term follow-up and the context of clinical outcome data, the balance of benefit and risk of anticoagulant therapy are challenging to mea-

*Editorials published in the *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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sure. Whereas the rather high rates of bleeding in this cohort are impressive, the fact that this study excluded patients who were transferred between hospitals as well as those who went on to coronary bypass surgery suggests that the true rate of major bleeding in the overall population is likely even higher (2).

Evidence-based guidelines encourage clinicians to calculate risk scores to facilitate clinical decisions regarding the intensity of pharmacological therapy and the need for and timing of invasive investigation and revascularization in ACS (10,11). Our own experience suggests that, despite the relative ease of calculating risk scores with handheld or online computer programs, there is limited use of risk scores in daily clinical practice. The additional value of a bleeding risk score to an “ischemic” risk score is debatable, because there is substantial overlap in the variables used for both. To demonstrate this we calculated—on a recent ACS patient in our coronary care unit—the GRACE (Global Registry of Acute Coronary Events) risk score (in-hospital death or myocardial infarction 21%) and CRUSADE bleeding risk score (in-hospital major bleeding 9.2%) (Fig. 1) (12). As will be evident, the same patient in whom an intensive pharmacological therapy and early aggressive invasive strategy is recommended is also at the highest risk of bleeding. Therefore, the frontline clinician receives a dilemma-

colored message regarding “optimal” care. A single integrated risk score that combines both efficacy and safety features would enhance decision-making for the practicing clinician.

Notwithstanding these limitations, the authors have provided an important and strikingly sober reminder of the risks of contemporary antithrombotic therapy in a population receiving concomitant antiplatelet agents and commonly undergoing invasive procedures. How promptly and how specifically feedback to individual contributing centers and practitioners is provided, given the likely but unknown heterogeneity of bleeding events across the 360 U.S. hospitals participating in this large registry, will be critical in achieving the desired quality improvement that such helpful registries are ultimately aimed at achieving. The recent emergence of updated American College of Cardiology/American Heart Association performance measures in ACS patients who emphasize oversight of excessive dosing of anticoagulants and the implementation of a tracking system of identifying dosing errors should prove helpful in this respect (13).

Acknowledgment

The authors would like to thank Jo-An Padberg for her excellent editorial assistance.

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REFERENCES

- Adam D, Carwardine M. Last Chance to See. Serious Productions Ltd. 1990.
- Kadakia MB, Desai NR, Alexander KP, et al., on behalf of the National Cardiovascular Data Registry. Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction: a report from the NCDR ACTION Registry-GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). *J Am Coll Cardiol Interv* 2010;3:1166–77.
- Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non ST-segment elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score. *Circulation* 2009;119:1873–82.
- Alexander KP, Peterson ED. Minimizing the risks of anticoagulants and platelet inhibitors. *Circulation* 2010;121:1960–70.
- Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation* 2005;112:3855–67.
- Ferguson JJ, Califf RM, Antman EM, et al., the SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy. *JAMA* 2004;292:45–54.
- Stone GW, McLaurin BT, Cox DA, et al., the ACUTITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203–16.

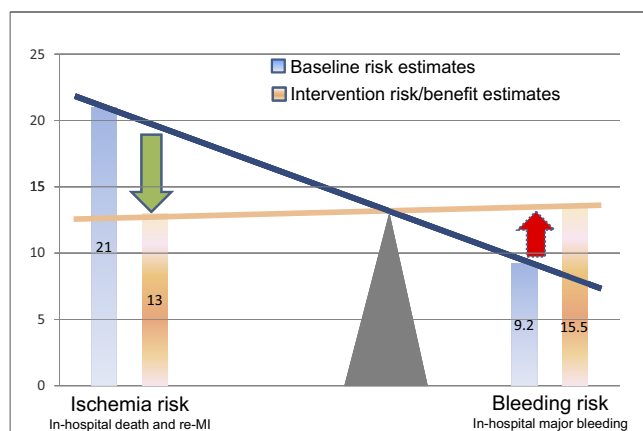


Figure 1. Baseline “Ischemia” Risk Assessment and Bleeding Risk

Baseline “ischemia” risk assessment (GRACE [Global Registry of Acute Coronary Events]) and bleeding risk (CRUSADE [Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines]) were calculated on a recent non-ST-segment elevation myocardial infarction (MI) patient (blue bar and line). Estimates of the benefit of implementing an intensive anticoagulation regime combined with an early invasive strategy were calculated on the basis of the high-risk population in the TIMACS (Timing of Intervention in Acute Coronary Syndrome) study (orange bar and line) (12). Estimates of the risk of implementing this regimen compared to a conservative pharmacological approach were calculated from the SYNERGY trial. The magnitude of benefit (green arrow) and risk of bleeding (red arrow) shift differentially depending on individual baseline patient characteristics, evolution of risk during hospital stay, anticoagulant strategy, and timing of invasive assessment.

8. Stone GW, Witzenbichler B, Guagliumi G, et al., the HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;358:2218-30.
9. Michaels AD, Spinler SA, Leeper B, et al., on behalf of the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, Council on Quality of Care and Outcomes Research; Council on Cardiopulmonary, Critical Care, Perioperative, and Resuscitation; Council on Cardiovascular Nursing and Stroke Council. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. *Circulation* 2010;121:1664-82.
10. Granger CB, Goldberg RJ, Dabbous O, et al., the Global Registry of Acute Coronary Events (GRACE) Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345-53.
11. Morrow DA, Antman EA, Charlesworth A, et al. Score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. *Circulation* 2000;102:2031-7.
12. Mehta SR, Granger CB, Boden WE, et al., the TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;360:2165-75.
13. Krumholz HM, Anderson JL, Bachelder BL, et al. Performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on performance measures (Writing Committee to Develop Performance Measures for ST-Elevation and Non-ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2008;52:2046-99.

Key Words: acute coronary syndrome ■ anticoagulant ■ invasive treatment ■ registries.